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RAKOCZY MOLINO MAZZOCHI SIWIK LLP
6 W. HUBBARD ST.
SUITE 500
CHICAGO, IL 60610

| EXAMINER | |
|---|---|
| KIM, JENNIFER M | |

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| 1628 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/584,661 | KOCSIS ET AL. | |
| | Examiner | Art Unit | |
| | JENNIFER M. KIM | 1628 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *6/21/2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-7 and 16-24* is/are pending in the application.

4a) Of the above claim(s) *5,7,12,13,15,17,21 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,16,18-20, 22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

The amendment filed June 21, 2010 have been received and entered into the application.

### Response to Arguments

Applicants' arguments filed June 21, 2010 have been fully considered but they are not persuasive. Applicants argue regarding the restriction requirement that was made final. It is examiner's position that the restrictions requirement still stands as final for the reasons stated in the previous Office Actions.

Applicant argues that the inventors unexpectedly discovered that when a selective serotonin uptake inhibitor is administered together with a sodium channel blocker to treat diseases involving chronic pain, epilepsy, and those diseases derived from disorders and/or injuries of the motor system, a marked increase in the sodium channel blocking activity is achieved. Thus, when administered in combination with a selective serotonin uptake inhibitor, the amount of sodium channel blocker needed to obtain a therapeutic effect is lower, allowing for a smaller dose, and this as a result reduces the known side effects associated with its administration. This is not persuasive because Applicants' data has been carefully reviewed and considered. The

"evidence" of alleged "potentiating effect" is not commensurate in scope with the breadth of the claims. It is well established that a showing of unexpected results generally must be commensurate in scope with the breadth of the claims sought to be patented. See, inter alia, (1) In re Greenfield, 571 F.2d 1185, 1189, 197 USPQ 227, 230 (CCPA 1978) (showing of unexpected results must be commensurate in scope with breadth of claim); (2) In re Kulling, 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1058 (Fed. Cir. 1990) (same); and (3) In re Lindner, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972) (same).

Applicant argues that the specification enables the prevention of conditions such as chronic pain and epileptic seizures because on page 10 of the specification as filed shows the data that pretreatment of selective serotonin uptake inhibitors and sodium channel blockers prior to inducing seizures inhibited the seizures, and thus the composition of the claimed invention are clearly enabled for preventing epileptic seizures. This is not persuasive because the instant specification particularly, page 10 has been carefully reviewed and considered. It teaches that pretreatment of the animals with SSRI compounds caused a substantial increase in the antiepileptic potency of the sodium channel blockers. However, there is no data showing Applicant's elected disorder of chronic pain (e.g. cancer pain) being prevented. Further, there is no statement or conclusive data that Applicants' alleged "prevention" of the seizure or epilepsy. Moreover, that sodium channel blockers such as lamotrigine increases the frequency of seizures in severe myoclonic epilepsy in view of Kaminska (2001). Arseneault et al. (U.S.Patent No. 4,614,499) teaches that a large number of patients

suffering from epilepsy, the disease cannot be controlled by medication and their only hope of cure is through surgery which rests in locating and destroying the epileptic area in the brain. However, unfortunately, the present operational technique still has a non-negligible limitations and the possibility of curing most epileptic patients remains a challenge. (column 1, lines 15-23). Shanthan (U.S.Patent No. 5,735,817) teaches that painful conditions, which affect our body, are difficult to treat, and it is especially true of most cancer pain. In some types of advanced cancers, the pain cannot be alleviated by any known method. Shantha also teaches that even with hundreds of milligrams of morphine administration, the pain could not be relieved (column 1, lines 1-30). Davar (U.S.Patent No. 6,667,832 B1) also teaches that the cancer pain is often debilitating and difficult to treat, especially in patients with advanced disease and the pain treatment often requires very large doses of either systemic or intraspinal opioids, often an insufficient pain treatment that produced undesirable side-effect (column 1, lines 62-column 2, line 10). To the extent that the instant claim is drawn to "prevention" which is highly speculative in view of the teaching from these prior art references, a greater amount of evidence is required to show it operability in humans. Therefore, the 35 U.S.C. 112, the first paragraph rejection (scope enablement) made in this Office Action is deemed proper.

Applicants argue that Fitzgerald et al makes no mention of coadministering an anti-conversant such as a sodium channel blocker, and an antidepressant, such as a selective serotonin uptake inhibitor. This is not found persuasive because such coadministration of a sodium channel blocker and an antidepressant for the treatment of

pain is obvious because there is a motivation for combining the components flows logically from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)). Applicants argue that Fitzgerald et al. teaches away from the use of selective serotonin uptake inhibitors with other drugs, due to "significant drug interactions". This is not persuasive because Fitzgerald et al's teaching that the selective serotonin uptake inhibitors have significant drug interactions with other drugs does not "teach away" from combining selective serotonin uptake inhibitor with a sodium channel blocker, but rather that caution is needed in selecting concomitant medication when combining with other unspecified drugs. There remains, even after the Fitzgerald et al's disclosure, a reasonable expectation of successfully treating chronic pain with combination of a sodium channel blocker and an antidepressant having the same analgesic activity. Applicants argue that there is little evidence to support the use of SSRI (such as fluoxetine, paroxetine, sertraline and venlafaxine) in the primary treatment of chronic pain. Therefore, Fitzgerald et al. would not have motivated one of skilled in the art to use a SSRI in a composition to be used to treat chronic pain. This is not persuasive because the motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)) in view of Fitzgerald.

Applicants argue that Coe et al. provides no data showing that any of their claimed compositions are effective for treating acute, chronic and/or neuropathic pain. This is not persuasive because Coe et al's teaching of reporting that sertraline is useful for the treatment of acute, chronic and/or neuropathic pain is enough to motivate one of

ordinary skill in the art to combine with another analgesic agent such as lamotrigine for the treatment of chronic pain to achieve at least an additive effect. Further, Carson et al. was cited to show that neuropathic pain is a chronic pain. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

### *Claim Rejections - 35 USC § 112*

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 24 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the "treatment " of disease such as chronic pain, epilepsy or injuries of the motor system, does not reasonably provide enablement for the "**prevention** of a disease occurring in a mammal". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

3. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors**

have been considered with regard to the instant claims, with the most relevant factors discussed below.

***Nature of the Invention***: The rejected claim is drawn to a method for the treatment and/or prevention of chronic pain or epileptic seizures, characterized in that a therapeutically effective amount of pharmaceutical composition comprising a sodium channel blocker and a selective serotonin uptake inhibitor is given to the subject in need of such treatment. The nature of the invention is extremely complex in that it encompasses the actual prevention of a disease occurring in a mammal involving chronic pain, motor system (i.e. cancer, multiple sclerosis) such that the subject treated with above compounds does not contract a disease occurring in a mammal.

***Breath of the Claims:*** The complex of nature of the claims greatly exacerbated by breath of the claims. The claims encompass **prevention** of a disease occurring in a mammal involving chronic pain, epilepsy or injuries of the motor system that can encompass a complex cell proliferation disorder or neurodegenerative disease in humans which has potentially many different causes (i.e. many different mutations or combination of mutations). Each of which may or may not be addressed by the administration of the claimed compounds.

***Working Examples:*** All of the working examples provided by the specification are directed toward the treatment rather than prevention of a disease occurring in a mammal.

***State of the Art:*** While the state of the art is relatively high with regard to treatment of a disease occurring in a mammal involving chronic pain (i.e. cancer), the state of the art with regard to **prevention** of such disease is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to **prevent** development of a disease occurring in a mammal. State of the art, Shanthan (U.S.Patent No. 5,735,817) teaches that painful conditions, which affect our body, are difficult to treat, and it is especially true of most cancer pain. In some types of advanced cancers, the pain cannot be alleviated by any known method. Shantha also teaches that even with hundreds of milligrams of morphine administration, the pain could not be relieved (column 1, lines 1-30). State of the art, Davar (U.S.Patent No. 6,667,832 B1) also teaches that the cancer pain is often debilitating and difficult to treat, especially in patients with advanced disease and the pain treatment often requires very large doses of either systemic or intraspinal opioids, often an insufficient pain treatment that produced undesirable side-effect (column 1, lines 62-column 2, line 10). Therefore, it is highly speculative that the active compounds would actually "prevent" the pain condition that is considered to be difficult in the treatment process.

***Predictability of the Art:*** The lack of significant guidance from the specification or prior art with regard to the actual **prevention** of a disease occurring in a human subject with the claimed compounds makes practicing the claimed

invention unpredictable in terms of prevention of a disease occurring in a mammal.

***The amount of Experimentation Necessary:*** In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed compounds and test the combination in the model system to determine whether or not the combination is effective for prevention of a disease occurring in a mammal. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regard prevention of a disease occurring in a mammal with any compound, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance form the specification of prior art regarding prevention of a disease occurring in a mammal with any compound, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to prevent the development of a disease occurring in a mammal by administration of one of the claimed compounds.

Therefore, a method for the prevention of a disease occurring in a mammal, said disease involving chronic pain, epilepsy or deriving from disorders and/or injuries of the motor system, characterized in that a therapeutically effective amount of pharmaceutical composition comprising a sodium channel blocker and a selective serotonin uptake inhibitor is given to the subject in need of such treatment is not considered to be enabled by the instant specification.

***Claim Rejections - 35 USC § 103***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-4, 6,16, 18-20, 22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fitzgerald et al. (1998) in view of Coe et al. (U.S. 2001/0036943A1) and further in view of Carson et al. (U.S.Patent No. 6,191,142 B1), all of record.

Fitzgerald et al. teach that lamotrigine is a novel anticonvulsant but effective in the management of chronic pain refractory to more conventional treatment. Fitzgerald et al. teach that the current indication of lamotrigine includes the treatment of neuropathic pain. (title, see under Lamotrigine). Fitzgerald et al. teach that the Lamotrigine is well absorbed after oral use with bioavailability approaching 80%. Fitzgerald et al. teach that the dosage of lamotrigine for the treatment of chronic pain at

25mg per day and increase by 25mg weekly until a dosage of 200mg per day is reached. (under Lamotrigine, pharmacokinetics and dose guidelines).

Fitzgerald et al. lack sertraline.

Coe et al. teach that sertraline is useful for the treatment of acute, chronic and/or neuropathic pain (abstract, claims 1 and 14).

Carson et al. report that neuropathic pain is defined as **pain** caused by aberrant somatosensory processing in the peripheral or central nervous system that is **chronic** or debilitating. (column 1, lines 21-30).

To employ combinations of lamotrigine and sertraline to treat chronic pain condition such as neuropathic pain would have been obvious because all the components are well known individually for treating chronic pain conditions such as neuropathic pain. It would be expected that the combination of components would treat chronic pain conditions such as neuropathic pain as well. The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)).

One of ordinary skill in the art would have combined the analgesic agents by known methods and that in combination, each element merely would have performed the same analgesic activity as it did separately. The convenience of putting the compounds having the same analgesic activity of lamotrigine and sertraline together in one dosage form, though perhaps a matter of great convenience does not produce a "new" or "different" function and to those skilled in the art, the use of the old elements in

combination would have been obvious. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

None of the claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

## Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER M. KIM whose telephone number is (571)272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JENNIFER M KIM/
Primary Examiner, Art Unit 1628

Jmk
August 12, 2010